Remarks

Reconsideration of this Application is respectfully requested.

Claims 1-6 and 11-16 are pending in the application, with claims 1 and 11 being the independent claims.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Entry of October 21, 2004 Claim Amendments

The Examiner indicated that the finality of the previous Office Action has been withdrawn and the Applicants' submission filed on June 14, 2005, has been entered. *See* Office Action, page 2. The Examiner, however, has not explicitly acknowledged that the amendments set forth in Applicants' Amendment and Reply Under 37 C.F.R. § 1.116, filed October 21, 2004, have been entered (although, from the Examiner's comments in the remainder of the Office Action, it appears that the claim amendments have been entered and considered). Clarification as to whether the amendments set forth in Applicants' October 21, 2004 response have been entered and considered is respectfully requested.

II. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

A. Enablement

Claims 1-5 and 11-15 were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. *See* Office Action, page 2. The basis for this rejection is the Examiner's position that:

> The nature and breadth of the claims encompass any method for identifying a test compound that inhibits the proteolytic activity of a separase using any substrate peptide comprising an [amino] acid sequence EXXR, wherein X is any amino acid. The specification provides guidance and working examples for the recited method using peptide substrates of SEQ ID NO: 9, SEQ ID NO: 11, and SEQ ID NO: 12.
>
> The specification nor the general knowledge of those skilled in the art do not provide guidance, prediction, and working examples showing that any of the 400 possible EXXR sequences shown on Exhibit 1 other than SEQ ID NOs: 9, 11, and 12 can be used as peptide substrates successfully in the claimed method. Thus, an undue amount of trial and error experimentation must be performed to search and screen for any peptide substrate including the 400 possible EXXR sequences shown on Exhibit 1 comprising the amino acid sequence EXXR which can be used in the method.

See Office Action, pages 2-3. Applicants respectfully disagree with the foregoing assertions and traverse this rejection.

First, the Examiner is reminded that, in order to establish a *prima facie* case of lack of enablement, the Examiner has the initial burden to set forth a reasonable basis to question the enablement provided for the claimed invention. *See In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). To satisfy this burden, "it is incumbent upon the Patent Office. . . to explain *why* it doubts the truth or accuracy of any statement in a

supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *See In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971) (emphasis in original).

Here, the Examiner's justification for the enablement rejection is that Applicants have allegedly failed to prove that peptides other than SEQ ID NOs: 9, 11 and 12 can be used as separase substrates in the practice of the claimed methods. No evidence or sound scientific reasoning, however, has been presented to suggest that only SEQ ID NOs: 9, 11 and 12 can be used as separase substrates or that it would have entailed anything more than routine experimentation for one of ordinary skill in the art to identify additional separase substrates having the sequence EXXR. The Examiner, therefore has not met his burden in establishing a *prima facie* case of lack of enablement.

Second, the reasoning presented in the above-quoted language is logically flawed. The mere absence of working examples of additional EXXR-containing separase substrates, besides SEQ ID NOs: 9, 11 and 12, does not lead to the conclusion that "an undue amount of trial and error experimentation must be performed to search and screen for any peptide substrate" having the sequence EXXR that can be used in the claimed methods. As noted in Applicants' previous response, making and testing numerous peptides containing the sequence motif EXXR and testing such peptides for the ability to be cleaved by separase, would have been routine. *See* Applicants' Supplemental Reply filed June 14, 2005, pages 5-7. No evidence or reasoning has been presented to contradict Applicants' assertions.

In addition, Applicants note that methods for screening and identifying enzyme substrates, in general, were well known and established in the art as of the effective filing

date of the present application. For example, Smith *et al.*, *J. Biol. Chem. 270*:6440-6449 (1995) (copy submitted herewith as Exhibit A) demonstrate a protease substrate screening method that uses bacteriophage-based peptide display libraries. Moreover, Cryns *et al.*, *J. Biol. Chem. 272*:29449-29453 (1997) (copy submitted herewith as Exhibit B) set forth a method that was used to identify caspase substrates using labeled protein pools derived from small cDNA library pools that had been transcribed/translated *in vitro*. Methods such as those set forth in Smith *et al.* and Cryns *et al.* could have been used by persons of ordinary skill in the art to identify separase substrates for use in the practice of the currently claimed methods. These references support Applicants assertion that making and identifying separase substrates would not have required undue experimentation.

It is well established in the law that:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention . . . must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support.

See Rasmusson v. Smithkline Beecham Corp., 413 F.3d 1318, 1323 (Fed. Cir. 2005) (quoting *Marzocchi*, 439 F.2d at 223). The Examiner has not presented any reason to doubt the objective truth of the statements in the present specification regarding the use of EXXR separase substrates in the practice of the claimed methods. Thus, under *Marzocchi* and later cases, the present specification "must be taken as in compliance with the enabling requirement of the first paragraph of § 112."

With regard to the teachings in the specification of methods for screening and identifying separase substrate peptides comprising the amino acids sequence EXXR, (*see, e.g.*, specification at page 9, lines 10-20), the Examiner has simply stated that:

> Teachings from the specification regarding screening and searching for the separase peptide substrates comprising the amino acid sequence EXXR is not guidance for making the claimed invention. Furthermore, searching and screening for the claimed invention is outside the realm of routine experimentation.

See Office Action, page 3. The Examiner has not explained why it is believed that the screening methods taught in the specification are "not guidance for making the claimed invention." The screening methods described in the specification would have enabled a skilled person to obtain the full range of EXXR-containing separase substrates that can be used in the practice of the claimed methods. Thus, the screening methods do indeed provide substantial guidance for practicing the claimed methods.

Moreover, the Examiner has not presented any evidence or sound scientific reasoning to support the assertion that the screening methods taught in the specification would have involved a level of difficulty that would amount to undue experimentation. Without any specific support, such assertions are legally insufficient to establish a *prima facie* case of lack of enablement.

Finally, the Examiner has asserted that "[w]hile applicants have presented 400 possible EXXR sequences shown on Exhibit 1, there is no presentation of non-naturally occurring amino acids (e.g., D-alloisoleucine) as well as different types of amino acid residue modifications including acylation as encompassed by the claims." *See* Office

Action, page 3. The Examiner has not explained why it is believed that separase substrates containing EXXR sequences with "non-naturally occurring" amino acids or modified amino acids would be unsuitable for use in the practice of the claimed methods. Moreover, the Examiner has not presented any evidence or reasoning to suggest that, if separase substrates containing EXXR sequences with "non-naturally occurring" amino acids or modified amino acids were unsuitable for use in the claimed methods, a person of ordinary skill in the art would not have been able to easily identify and reject such inoperable substrates using routine screening methods. Applicants submit that the screening methods presented in the specification and available in the art (*see, e.g.*, Smith *et al.* and Cryns *et al.*) would have enabled a skilled person to easily and routinely identify suitable EXXR-containing separase substrates, even among those that include "non-naturally occurring" amino acids or modified amino acids. No evidence to the contrary has been presented.

Since no evidence or sound reasoning has been presented to indicate that identifying and using separase substrates comprising an amino acid sequence EXXR would have involved anything more than the application of routine techniques, a *prima facie* case of lack of enablement has not been presented. Applicants respectfully request that this rejection be reconsidered and withdrawn.

B. Written Description

Claims 1-5 and 11-15 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. *See* Office Action, page 3. According to the Examiner:

> The scope of the genus includes many peptides with widely differing amino acid sequences as well as widely differing structural, chemical and biophysical properties. The scope of the genus is not limited to peptides "consisting" of EXXR, SEQ ID NO: 9, 11, or 12 since the claims specifically recite the phrase "comprising an amino acid sequence".

See Office Action, page 4. Applicants respectfully traverse this rejection for the reasons set forth in the Supplemental Reply filed on June 14, 2005. In addition, Applicants present the following comments which further demonstrate that a *prima facie* case of lack of written description has not been established.

The Examiner appears to believe that the written description requirement necessarily requires that, for every element generically recited in a claim, the specification must disclose a structure common to every possible species of the recited generic element. *See* Office Action, page 4. In the Examiner's words, "[t]he specification does not provide a description of an amino acid sequence and structure common to the members of the claimed genus of peptides comprising the amino acid sequence EXXR . . ." *See* Office Action, page 4.

The Examiner's application of the written description requirement in this context is legally incorrect. First, contrary to the Examiner's statement, the claims are not directed to a genus of peptides comprising the amino acid sequence EXXR. The claims are directed to *methods* that include the use of separase substrates comprising an amino acid sequence EXXR. This is a critical distinction that must be taken into account when assessing compliance with the written description requirement. *See* discussion presented below.

When generic elements of a claim (*e.g.*, separase substrates comprising the amino acid sequence EXXR) are so well known and thoroughly characterized in the art that their

recitation alone is sufficient to convey distinguishing information regarding their identity, the written description requirement for those elements is fully satisfied. *See, Amgen Inc. v. Hoechst Marion Roussel Inc.*, 65 U.S.P.Q.2d 1385, 1398 (Fed. Cir. 2003). Since the written description issue in *Amgen* is very similar to the written description issue raised in the present Office Action, a brief discussion of the *Amgen* case is presented below and a copy of the case is provided herewith as Exhibit C.

In *Amgen*, the claims at issue were directed to methods for producing a glycosylated erythropoietin polypeptide. *See Amgen* at 1390. The claimed methods included, *inter alia*, the step of "growing, under suitable nutrient conditions, *vertebrate cells* comprising amplified DNA encoding the mature erythropoietin amino acid sequence of FIG. 6." *See id.* Also at issue were dependent claims that specified that the cells were *mammalian cells*. *See Amgen* at 1391. Just as separase substrates comprising an amino acid sequence EXXR in the present claims are not being claimed *per se*, the claims at issue in *Amgen* were not directed to vertebrate cells or mammalian cells *per se*. Rather, the cells were simply an element used in the practice of the claimed methods.

The defendants in *Amgen* asserted that the claims lacked adequate written description because "Amgen failed to sufficiently describe the use of all vertebrate and mammalian cells." *See Amgen* at 1397. Like the Examiner in the present case, the defendants in *Amgen* cited *University of California v. Eli Lilly and Co.* 43 USPQ 2d 1398 (Fed. Cir. 1997) to support the assertion of inadequate written description. *See Amgen* at 1398. The Federal Circuit made it clear, however, that *Eli Lilly* does not apply when, as here, the subject matter

in question is well known and fully appreciated by persons of ordinary skill in the art. According to the court:

> the claim terms at issue here are not new or unknown biological materials that ordinary skilled artisans would easily miscomprehend. Instead, the claims of Amgen's patents refer to types of cells that can be used to produce recombinant human EPO...*the words "vertebrate" and "mammalian" readily "convey[] distinguishing information concerning [their] identity" such that one of ordinary skill in the art could "visualize or recognize the identity of the members of the genus.*" Indeed, the district court's reasoned conclusion that the specification's description of producing the claimed EPO in two species of vertebrate or mammalian cells adequately supports claims covering EPO made using the genus of vertebrate or mammalian cells, renders *Eli Lilly* listless in this case.

Id. at 1398 (internal citations omitted, emphasis added).

Thus, even though Amgen's patents described only "two species of vertebrate or mammalian cells," the Federal Circuit found such disclosure to provide adequate written description support for the entire genus of vertebrate or mammalian cells used to produce EPO according to the claimed methods. The court's decision was based on two principle factors:

1. That the claim terms at issue ("vertebrate" and "mammalian") did *not* refer to new or unknown biological materials that ordinary skilled artisans would easily miscomprehend; and
2. That the words "vertebrate" and "mammalian," as used in the claims, readily conveyed distinguishing information concerning their identity such that one of ordinary skill in the art could visualize or recognize the identity of members of the genus.

When the reasoning of *Amgen* is applied in the context of the present claims, it is clear that the written description requirement is more than adequately satisfied for separase substrates comprising an amino acid sequence EXXR.

First, the expression "separase substrate comprising an amino acid sequence EXXR," like the terms "vertebrate" and "mammalian," does not refer to new or unknown biological materials that ordinary skilled artisans would easily miscomprehend. Separase substrates comprising the amino acid sequence EXXR were well known and characterized prior to the effective filing date of the present application. *See* Applicants' Supplemental Reply filed June 14, 2005, pages 8-9, and Exhibits 4-6, submitted therewith. Accordingly, at the time of the effective filing date of the present application, separase substrates comprising the amino acid sequence EXXR certainly were not new or unknown biological materials.

Second, the expression "separase substrate comprising the amino acid sequence EXXR" readily conveys distinguishing information concerning the identity of the substrates so that persons of ordinary skill in the art could recognize the identities of members of the genus. Persons of ordinary skill in the art would readily understand from the claim terms alone that the substrates used in the practice of the claimed methods (a) include the EXXR amino acid motif, and (b) are capable of being cleaved by the active separase. Thus, a skilled person would be able to readily distinguish the separase substrates used in the practice of the claimed methods from peptides that fall outside the scope of the claim language (*i.e.*, peptides that lack the EXXR amino acid motif and/or are not capable of being cleaved by an active separase).

In *Amgen*, the specification at issue disclosed two species of vertebrate or mammalian cells and was held to provide adequate written description support for these genuses. Here, the specification discloses several exemplary EXXR-containing separase substrates, including peptides comprising the amino acid sequences of SEQ ID NOs: 9, 11 and 12, as well as the budding yeast protein SCC1 and fragments thereof. *See* specification at page 7, lines 9-13, and at page 21, lines 8-10.

There is no indication that the inventors intended to limit in any way the kinds of separase substrates that could be used in the claimed methods. Just as a person of ordinary skill in the art would have appreciated that the invention at issue in *Amgen* included the use of *any* vertebrate or mammalian cell to produce EPO, a person of ordinary skill in the art would have appreciated that the present invention includes the use of *any* separase substrate comprising the amino acid sequence EXXR that is capable of being cleaved by active separase.

The Examiner's attention is also directed to Example 18 of the USPTO's "Synopsis of Application of Written Description Guidelines" (available at http://www.uspto.gov/web/menu/written.pdf, copy submitted herewith as Exhibit D). This Example illustrates an analysis of the written description provided for a process claim where the novelty is in the method steps. The claim at issue in this Example is as follows:

> A method of producing a protein of interest comprising;
>
> obtaining *Neurospora crassa* mitochondria,
>
> transforming said mitochondria with a expression vector comprising a nucleic acid that encodes said protein of interest,

> expressing said protein in said mitochondria, and
> recovering said protein of interest.

The specification shows actual reduction to practice of a single embodiment: the expression of β-galactosidase. The claimed process, however, involves the use of *any* nucleic acid that encodes *any* protein of interest, a virtually unlimited genus. Nonetheless, the Example concludes that the claimed invention is adequately described. According to the analysis provided in this Example:

> The art indicates that there is no substantial variation within the genus because there are a limited number of ways to practice the process steps of the claimed invention.
>
> The single embodiment is representative of the genus based on the disclosure of *Neurospora crassa* mitochondria as a gene expression system, considered along with the level of skill and knowledge in the gene expression art. One of skill in the art would recognize that applicant was in possession of all of the various expression methods necessary to practice the claimed invention.

Significantly, in assessing the written description of this hypothetical claim, the USPTO's Example does not even question whether the specification provides adequate description of the entire genus of nucleic acid encoding a protein of interest because the nucleic acid is *not itself being claimed.* Thus, the analysis properly focuses on whether the *process* is adequately described, not whether the individual elements used in the practice of the process (*e.g.*, the different types of nucleic acids) are adequately described.

Analogously, separase substrates comprising the amino acid sequence EXXR in the present claims are not themselves being claimed; they are simply elements used in the practice of the claimed methods. Thus, the written description analysis should focus on

whether or not the *methods* are adequately described, not whether separase substrates comprising the amino acid sequence EXXR are adequately described (although they certainly are adequately described, as noted above and in Applicants' previous responses).

Moreover, Example 18 of the USPTO's Guidelines emphasizes the need to consider the level of skill and knowledge in the relevant art in assessing adequacy of written description. As discussed previously, the level of skill and knowledge in the art concerning separase substrates was high, especially considering that multiple substrates had been identified and characterized at the time of the effective filing date of the present application. (The Examiner has not presented any evidence to suggest that the level of skill and knowledge in the art of separase substrates was not high.) The high level of skill and knowledge in the art reinforces the conclusion that the written description requirement is fully satisfied for the currently presented claims.

The Examiner's application of the written description requirement in the present case appears to assume that separase substrates comprising the amino acid sequence EXXR are new compounds that are being directly claimed; however, as mentioned above, this is not the case. Numerous species of separase substrates comprising the amino acid sequence EXXR had been identified and studied prior to the effective filing date of the present application. Persons of ordinary skill in the art would clearly appreciate and visualize the full range of separase substrates included in the practice of the present claims without any need for disclosure of common structural characteristics beyond the recitation of the EXXR sequence. The present claims are directed to *methods* that involve the use of such substrates. The Examiner's basis for rejecting the claims due to an alleged lack of description of "an amino

acid sequence and structure common to the members of the claimed genus of peptides comprising the amino acid sequence EXXR" is therefore legally improper.

In view of the current state of the law on adequacy of written description (*e.g.*, *Amgen*) and the USPTO's own guidelines on this topic, it must be concluded that the written description requirement of § 112, first paragraph, is fully satisfied for the currently presented claims. Applicants respectfully request that this rejection be reconsidered and withdrawn.

III. Claim Objections

Claims 6 and 16 were objected to as being dependent upon a rejected base claim. Since the rejections of claims 5 and 15, from which claims 6 and 16 respectively depend, was in error, it follows that the objections to claims 6 and 16 are also in error and should be withdrawn.

Conclusion

All of the stated grounds of objections and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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